NKDEP
National Kidney Disease Education Program

Creatinine Standardization Program

Recommendations for Clinical Laboratories*

The National Kidney Disease Education Program (NKDEP), in collaboration with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Communities Confederation of Clinical Chemistry (EC4), has launched the Creatinine Standardization Program to reduce inter-laboratory variation in creatinine assay calibration and provide more accurate estimates of glomerular filtration rate (GFR). The effort is part of a larger NKDEP initiative to help healthcare providers better identify and treat chronic kidney disease in order to prevent or delay kidney failure and improve patient outcomes.

Clinical laboratories are crucial partners in the successful implementation of this program. The following steps are necessary to ensure a smooth transition from traditional calibration of routine creatinine methods to calibration that is traceable to an isotope dilution mass spectrometry (IDMS) reference method:

1) Continue using the original Modification of Diet in Renal Disease (MDRD) Study equation for routine methods that have *not* been calibrated to be traceable to IDMS. It is appropriate to use this equation because most methods in this category will produce creatinine results that have a bias similar to that of the method used in developing the original MDRD Study equation. If you have any question about the traceability of the calibration for the creatinine method in use by your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.
2) Coordinate with your creatinine method provider so that you immediately begin using the IDMS-traceable MDRD Study equation for estimating GFR when using a creatinine method that has its calibration traceable to IDMS. During the transition to IDMS-traceable calibration, methods that produce results that have acceptable bias [as defined in *Clinical Chemistry* 2006;52(1):5-18] when compared to an IDMS-traceable method also should use the IDMS-traceable MDRD Study equation.
3) Report estimated GFR (eGFR) values above 60 mL/min/1.73 m^2 as ">60 mL/min/1.73 m^2" and not as an exact number. For values 60 mL/min/1.73 m^2 and below, the report should give the numerical estimate rounded to the nearest whole number (e.g., 35 mL/min/1.73 m^2).
4) When calculating an eGFR, use serum creatinine values as mg/dL to two decimal places, or as µmol/L to the nearest whole number. This will reduce the contribution of rounding error when using the MDRD Study equation.
5) When using a creatinine method that is traceable to IDMS, report PT/EQAS results for serum and urine creatinine using the correct instrument/method peer group for IDMS-traceable calibration. IVD manufacturers and NKDEP are cooperating to inform PT/EQAS providers of the participant grading issues during the transition to standardized creatinine methods. (See *Recommendations for Proficiency Testing and External Quality Assessment Scheme Providers* available at www.nkdep.nih.gov/labprofessionals.)
6) Communicate the following clinical issues to healthcare providers, including pharmacists, when using a serum creatinine method that has its calibration traceable to an IDMS reference method.
    - Provide a serum creatinine reference interval that is appropriate for the method.

* These recommendations update those originally published in *Clinical Chemistry* 2006;52(1):5-18.

- Creatinine clearance values based on measured serum and urine creatinine results may change and a new reference interval and interpretive criteria may need to be established for creatinine clearance. The effect on measured creatinine clearance will vary depending on the procedure used to calibrate serum and urine measurements.

- For most patients, an eGFR using the MDRD Study equation is more accurate than a creatinine clearance calculated from serum and urine measurements. Therefore, NKDEP recommends not performing a measured creatinine clearance procedure for adults except when the patient's basal creatinine production is very abnormal. This may be the case with patients of extreme body size or muscle mass (e.g., obese, severely malnourished, amputees, paraplegics or other muscle-wasting diseases) or with unusual dietary intake (e.g., vegetarian, creatine supplements).

- The clinical laboratory should notify the pharmacy and drug prescribers to inform them of the expected magnitude of change in serum creatinine values, and whether the creatinine clearance measured from serum and urine will be affected by the change. Serum creatinine and algorithms to estimate kidney function are used to adjust the doses of drugs. Creatinine methods with calibration traceable to IDMS may have large enough changes in creatinine values that drug dose algorithms will be affected. For additional information, refer to the *Recommendations for Pharmacists and Authorized Drug Prescribers* available at www.nkdep.nih.gov/labprofessionals.

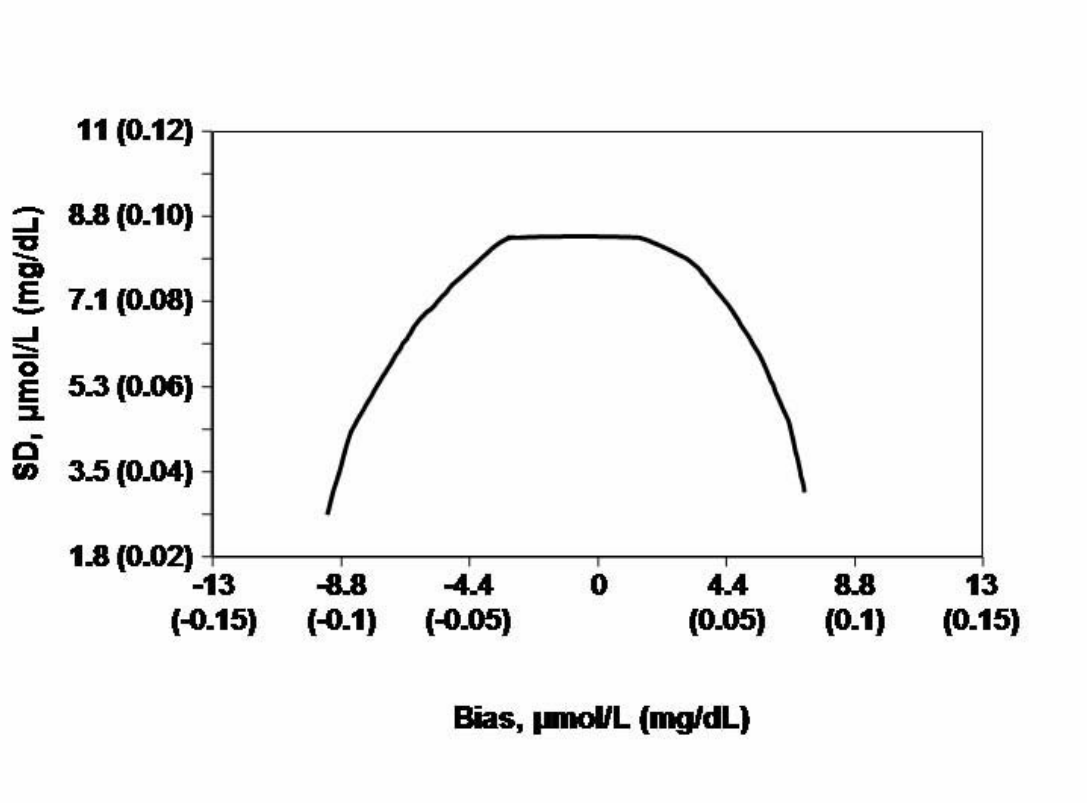
    - IVD manufacturers need to provide the necessary information to clinical laboratories regarding the relationship between serum and urine creatinine results measured with an IDMS-traceable method and older methods that used traditional calibration. Manufacturers should provide detailed descriptions (including mathematical conversion factors, equations, or functions) of the impact of their calibration changes, for both serum and urine creatinine values, with emphasis on the serum 0.5 to 2.5 mg/dL (45 to 220 µmol/L) range of interest. This will ensure that customers or labs using any of the pharmacy drug dosing approaches can adjust IDMS-traceable creatinine values for use with appropriate legacy dosing reference tables and algorithms (such as serum creatinine value, eGFR or creatinine clearance based on estimating equations from serum creatinine, or traditional measured creatinine clearance from serum and urine values).

- Following implementation of serum creatinine methods with calibration traceable to IDMS, other equations used to estimate kidney function, such as Cockcroft-Gault, Schwartz, or Counahan-Barratt, will give values that, in most cases, are higher than the values obtained using traditionally calibrated creatinine methods. This change will affect interpretive criteria based on these estimates of kidney function.

- Creatinine measurements at the low values usually observed in pediatric patients have a greater measurement variability than for values seen in adults. Estimates of kidney function based on these values also will have greater variability than for adults.

7) When using a creatinine method that has its calibration traceable to IDMS, a realistic total error goal for serum creatinine measurement is described by Figure 3 in the paper published in *Clinical Chemistry* 2006;52(1):5-18 (reproduced in the figure below). This figure provides an error budget for creatinine measurement in the range 1.00-1.50 mg/dL (88.4-133 µmol/L) that will ensure less than 10% increase in the relative error of the eGFR. An example of method performance that would achieve this total error goal is analytical imprecision (including inter-laboratory calibration

variability) SD <0.08 mg/dL (7.1 µmol/L) and analytical bias (compared to an IDMS reference measurement procedure) <0.05 mg/dL (4.4 µmol/L) at a serum creatinine concentration of 1.00 mg/dL (88.4 µmol/L).



8) The College of American Pathologists' LN24 Survey (commutability validation pending), or comparable EQA with commutable samples and IDMS target values, may be useful to monitor calibration performance of routine methods that have calibration traceable to an IDMS reference method.

Information about the Creatinine Standardization Program and recommendations for other groups, including IVD manufacturers, is available at www.nkdep.nih.gov/labprofessionals.

Contact Information

For assistance, please contact us at csp@info.niddk.nih.gov or call 301-435-8116.

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